

Perspective Piece

Rationale for the Coadministration of Albendazole and Ivermectin to Humans for Malaria Parasite Transmission Control

Kevin C. Kobylinski,* Haoues Alout, Brian D. Foy, Archie Clements, Poom Adisakwattana, Brett E. Swierczewski, and Jason H. Richardson

Entomology Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland; Arthropod-Borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, Colorado; Research School of Population Health, The Australian National University, Canberra, Australian Capital Territory, Australia; Department of Helminthology, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; Bacterial Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland; Deployed Warfighter Protection Program, Armed Forces Pest Management Board, Silver Spring, Maryland

Abstract. Recently there have been calls for the eradication of malaria and the elimination of soil-transmitted helminths (STHs). Malaria and STHs overlap in distribution, and STH infections are associated with increased risk for malaria. Indeed, there is evidence that suggests that STH infection may facilitate malaria transmission. Malaria and STH coinfection may exacerbate anemia, especially in pregnant women, leading to worsened child development and more adverse pregnancy outcomes than these diseases would cause on their own. Ivermectin mass drug administration (MDA) to humans for malaria parasite transmission suppression is being investigated as a potential malaria elimination tool. Adding albendazole to ivermectin MDAs would maximize effects against STHs. A proactive, integrated control platform that targets malaria and STHs would be extremely cost-effective and simultaneously reduce human suffering caused by multiple diseases. This paper outlines the benefits of adding albendazole to ivermectin MDAs for malaria parasite transmission suppression.

A CALL FOR ERADICATION, ELIMINATION, AND INTEGRATION

There have been recent calls for the eradication of malaria¹ and suggestions of soil-transmitted helminth (STH) elimination by shifting from morbidity control to transmission control.^{2,3} Numerous publications call for the integration of control measures that target malaria and neglected tropical diseases (NTDs) with the same platform.^{4–9} The NTDs are a diverse group of infectious diseases including STH infections, lymphatic filariasis (LF), schistosomiasis, onchocerciasis, and at least 13 others, prioritized by the World Health Organization as such, because they promote poverty and have a negative impact on pregnancy, child health and development, and adult worker productivity. Examples of synergism between malaria and NTD control programs include a reduction in LF transmission by the large-scale rollout of long-lasting insecticide-treated nets (LLINs) and indoor residual spraying (IRS) with insecticides for malaria control^{10,11} and the distribution of LLINs and sulfadoxine-pyrimethamine for intermittent preventive therapy for pregnant women by Community-Directed Treatment (CDT) platforms that have been mobilized by the African Program for Onchocerciasis Control (APOC)^{12,13} and the Global Program to Eliminate Lymphatic Filariasis (GPELF)¹⁴ in Africa. Indeed, Nigeria has recently announced a nationwide integration of malaria and LF elimination efforts, which will use the CDT platform to enhance LLIN distribution and communication of education messages that promote LLIN use. However, reports of successful integration of malaria elimination and STH control efforts are lacking.

Both the APOC and GPELF in Africa have strategically used mass drug administration (MDA) by CDT with ivermec-

tin to deliver more than 300 million treatments annually (www.mectizan.org) to suppress the transmission of *Onchocerca volvulus* and *Wuchereria bancrofti* microfilariae to their respective insect vectors. Ivermectin MDA to all eligible persons in a given area offers promise as a potential vector-targeted measure to reduce *Plasmodium* transmission because of the lethal and sublethal effects of ivermectin against numerous *Anopheles* vectors.¹⁵ Sustained *Plasmodium* transmission suppression would likely require repeated ivermectin MDAs spaced across transmission seasons.^{16,17} In Nigeria, annual APOC-coordinated ivermectin MDAs have shown a significant reduction in prevalence of the STHs *Ascaris lumbricoides* and *Trichuris trichiura* but not hookworm.¹⁸ Ivermectin exerts strong activity against *Ascaris*, moderate activity against *Trichuris*, and minimal to no effect against hookworm. Albendazole, a benzimidazole anthelmintic, has strong effect against *Ascaris* and hookworm and moderate effect against *Trichuris*.¹⁹ The combination of both ivermectin and albendazole is superior to either drug alone for the treatment of the STHs, especially *Trichuris*.^{19–23} Gutman and others¹⁸ conclude that the addition of albendazole to ivermectin MDAs would increase effects against STHs, because the MDA would have a greater impact against hookworms. Indeed, part of the rationale for the addition of albendazole for LF elimination by the GPELF was the secondary effects on STHs.²⁴ In support, analysis of health records in Zanzibar showed that six rounds of GPELF-coordinated ivermectin and albendazole MDAs led to dramatic reductions in reported STH and scabies infections.²⁵ The coadministration of albendazole and ivermectin is safe and well-tolerated, and the combination is given to millions of people annually by the GPELF in Africa.²⁶

In sub-Saharan Africa, there is extensive overlap in the distribution of STHs and *P. falciparum*,^{27–29} which provides opportunities to target STHs and malaria with the same ivermectin and albendazole MDA platform. In addition to STHs, expanded ivermectin and albendazole MDAs for malaria elimination would aid onchocerciasis control and LF elimination

* Address correspondence to Kevin C. Kobylinski, Entomology Department, Armed Forces Research Institute of Medical Sciences, 315/6 Rajvithi Road, Bangkok, Thailand 10400. E-mail: kobylinskikevin@yahoo.com

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 2014		2. REPORT TYPE		3. DATES COVERED 00-00-2014 to 00-00-2014	
4. TITLE AND SUBTITLE Rationale for the Coadministration of Albendazole and Ivermectin to Humans for Malaria Parasite Transmission Control				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Walter Reed Army Institute of Research, Entomology Branch, 503 Robert Grant Ave, Silver Spring, MD, 20910				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Recently there have been calls for the eradication of malaria and the elimination of soil-transmitted helminths (STHs). Malaria and STHs overlap in distribution, and STH infections are associated with increased risk for malaria. Indeed, there is evidence that suggests that STH infection may facilitate malaria transmission. Malaria and STH coinfection may exacerbate anemia, especially in pregnant women, leading to worsened child development and more adverse pregnancy outcomes than these diseases would cause on their own. Ivermectin mass drug administration (MDA) to humans for malaria parasite transmission suppression is being investigated as a potential malaria elimination tool. Adding albendazole to ivermectin MDAs would maximize effects against STHs. A proactive, integrated control platform that targets malaria and STHs would be extremely cost-effective and simultaneously reduce human suffering caused by multiple diseases. This paper outlines the benefits of adding albendazole to ivermectin MDAs for malaria parasite transmission suppression.					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Same as Report (SAR)	18. NUMBER OF PAGES 8	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

efforts as well as affect numerous other NTDs found worldwide, including strongyloidiasis,³⁰ gnathostomiasis,³¹ pediculosis, and scabiasis.³² Targeting multiple diseases with the same MDA platform will likely help maintain high compliance levels, because treated individuals will readily observe direct personal effects³³ in addition to the community-level effect of reduced *Plasmodium* transmission. This paper will outline the proposed benefits of adding albendazole to ivermectin MDAs for malaria and STH parasite transmission elimination efforts.

STHS MAY FACILITATE *PLASMODIUM* TRANSMISSION

There is mounting evidence that infection with STHs is associated with increased risk for malaria infection. A recent meta-analysis of the published malaria and STH coinfection literature found that hookworm infection is a risk factor for malaria in pregnant women and that any STH infection is a risk factor for malaria in school-aged children.³⁴ *Ascaris* infection was found to be a risk factor for *P. falciparum* infection in school-aged children in Nigeria,³⁵ pregnant women in Ghana³⁶ and Gabon,³⁷ and people of all ages in Ethiopia.³⁸ *Trichuris* infection was a risk factor for *P. falciparum* infection for all ages in Ethiopia.³⁸ Hookworm infection was a risk factor for *P. falciparum* infection in pre-school-aged children, adults,³⁹ and pregnant women⁴⁰ in Uganda, people of all ages in Colombia,⁴¹ and school-aged children in Cote d'Ivoire,⁴² Zimbabwe,⁴³ and Ghana,⁴⁴ and it was a risk factor for pregnant women along the Thai-Myanmar border for both *P. falciparum* and *P. vivax* infection.⁴⁵ Any STH infection was a risk factor for *P. falciparum* in pre-school-aged and school-aged children in Senegal,⁴⁶ school-aged children in Nigeria,³⁵ and people of all ages in Ethiopia.³⁸ In Thailand, people infected with a single STH had a higher risk of *P. falciparum* infection, and this risk increased as the number of STH species per person increased.⁴⁷ This finding was also true in Ethiopia for *Ascaris* and *Trichuris* coinfections and *Ascaris*, *Trichuris*, hookworm, and *Schistosoma mansoni* coinfections.⁴⁸ Although numerous publications have documented no increased risk of *Plasmodium* infection associated with STH infection, there have been only two published negative associations that we are aware of including, *P. falciparum* and *Ascaris* infections in pregnant women along the Thai-Myanmar border⁴⁵ and *P. falciparum* and hookworm infections in young, non-pregnant women in Cote d'Ivoire.⁴²

Aside from coinfection risk factors, there may be other consequences of STH infection that could enhance *Plasmodium* transmission. *Ascaris*-infected people were more likely to have contemporaneous and successive mixed species infections of *P. falciparum* and *P. vivax*,⁴⁹ which may increase *Plasmodium* transmission, because coinfections increase the frequency of *P. falciparum* gametocyte carriage.^{50–52} *Trichuris*-infected individuals were more likely to have multiple *P. falciparum* clones,⁵³ which may affect *Plasmodium* transmission to mosquitoes. Any STH infection was shown to be associated with increased *P. falciparum* gametocyte carriage rates, and an increasing number of STH species in infected people may be associated with increased gametocyte carriage rates.⁵⁴ It has been suggested that STH-infected individuals in resource-poor settings may not seek medical treatment even when coinfecting with *Plasmodium* parasites, thus acting as a low-profile transmission hub for gametocytes. Because much of

this research has been performed in clinical settings, future field trials in various ecological settings will be required to assess whether STHs do enhance *Plasmodium* transmission from asymptomatic individuals.⁵⁵

These studies show that STH infection might influence *Plasmodium* transmission, which suggests that STH control alone may reduce *Plasmodium* transmission. Indeed, in Nigeria, it was shown that albendazole MDA every 4 months for 12 months to children (12–59 months old) reduced the prevalence and intensity of *A. lumbricoides*,⁵⁶ and although both albendazole and placebo-treated groups had an increase in *Plasmodium* infection odds over time, this increase was significantly slower in the albendazole-treated group.⁵⁷ This work suggests that albendazole MDA may impact malaria transmission, possibly by reducing *A. lumbricoides* prevalence and intensity. Thus, integration of malaria and STH elimination programs may accelerate regional malaria elimination efforts.

EXPECTED HEALTH AND DEVELOPMENT IMPACTS ON MALARIA AND STH REDUCTION

Numerous investigations have shown a protective effect of STHs from severe malaria manifestations (e.g., cerebral malaria),^{58,59} whereas others have shown exacerbating effects of STHs on severe malaria.^{46,60} The protective or exacerbating effects of STHs on development of severe malaria are highly debatable and may be influenced by several factors, including study location and design, the STH species investigated, STH prevalence and intensity, malaria case definitions, or the anthelmintic drugs investigated.^{61,62} The argument that the removal of STHs from local populations may exacerbate malaria severity is controversial. If the goal is malaria elimination and this goal is being regionally achieved, then it is not logical to maintain detrimental STH infections in these same populations for the sake of debatable protective effects of STHs on severe malaria.

Concomitant infection with *Plasmodium* and STHs, particularly hookworm, can exacerbate anemia in non-pregnant and pregnant adults,^{34,63} which leads to worsened child development⁶⁴ and more adverse pregnancy outcomes^{36,65} than these diseases would cause on their own. Reduction in malaria and STH prevalence would positively impact child growth rates, school attendance, cognitive development, and adult labor force participation,^{20,66,67} which would allow malaria- and STH-afflicted populations a better opportunity to escape the cycle of poverty.⁶⁸ In Nepal, albendazole treatment of pregnant women during their second and third trimesters reduced the rate of severe anemia in pregnant women, increased infant birth weight, and reduced infant mortality.⁶⁹ Limited studies show that treatment of pregnant women with both ivermectin and albendazole seems to be safe for the mother and the fetus,^{70,71} and thus, the benefit of treating STH infections in pregnant women may outweigh perceived risks of treatment with these drugs.

IVERMECTIN AND ALBENDAZOLE MDA IMPACTS ON MALARIA PARASITE TRANSMISSION

Ivermectin binds at subunit interfaces next to the pore of the glutamate-gated chloride (GluCl) ion channels, which distorts the channel from a closed to open state, thus hyperpolarizing

the cell⁷² leading to flaccid paralysis of ectoparasite musculature.⁷³ *Plasmodium* parasites do not have GluCl channels, and ivermectin is not effective against blood-stage *P. falciparum* at human-relevant concentrations either *in vitro*⁷⁴ or *in vivo*.⁷⁵ However, ivermectin can affect numerous factors of vectorial capacity for *Plasmodium* transmission, including reducing *An. gambiae* s.s. survivorship and recovery after a blood meal,^{76–79} delaying mosquito refeeding,⁷⁸ and inhibiting the development of *P. falciparum* in the mosquito (i.e., sporontocidal).⁸⁰ Furthermore, we have shown that ivermectin MDA to humans in Senegalese villages reduced wild *An. gambiae* s.s. survivorship up to 1 week post-MDA¹⁶ and reduced the proportion of *P. falciparum*-infectious *An. gambiae* s.s. up to 2 weeks post-MDA.⁸¹ Ivermectin MDA fulfills many of the demands for novel vector-targeted interventions put forth by the malaria eradication research agenda for vector control.^{15,82} Although there is mounting evidence that ivermectin MDAs may suppress *Plasmodium* transmission, well-designed clinical trials showing sufficient effect in diverse transmission settings must occur before ivermectin MDAs can be recommended for implementation by national malaria control programs and supported by global public health funding agencies.

Albendazole belongs to the class of benzimidazole anthelmintics that are active against blood-stage *P. falciparum* *in vitro*^{83,84} and *P. berghei* *in vivo*^{85,86} but not at human-relevant concentrations. The benzimidazoles are microtubule inhibitors known as colchicine-site binders that bind to β -tubulin, inhibiting its polymerization and subsequent spindle formation during mitosis and thereby interfering with cellular division and schizogony of *Plasmodium*.^{87,88} There may be several points during both blood- and mosquito-stage *Plasmodium* cycles at which benzimidazoles may inhibit microtubule assembly, including micro- and macrogametocytogenesis, microgamete exflagellation, and the development, integrity, and motility of sporogonic forms in the mosquito.⁸⁷

To assess whether albendazole is sporontocidal, two experiments were performed with *An. gambiae* (G3 strain) and *P. falciparum* (NF54 strain) using the previous methodology in the work by Kobylinski and others⁸⁰ that showed the sporontocidal effect of ivermectin. We tested albendazole sulfoxide, the primary metabolite of albendazole, because albendazole is rapidly converted to its primary metabolite⁸⁹ by the time that night-feeding *Anopheles* would ingest a blood meal from an albendazole-treated person. For the experiment testing only albendazole sulfoxide (Sigma Aldrich, St. Louis, MO), mosquito blood meals contained vehicle alone (control) and either 1,000 or 100 ng/mL albendazole sulfoxide and were fed to mosquitoes concomitantly with *P. falciparum* gametocytes. For the experiment testing the sporontocidal effect of albendazole sulfoxide and ivermectin coingestion, blood meals containing vehicle alone (control), 10.7 ng/mL ivermectin (Sigma Aldrich), or 10.7 ng/mL ivermectin with 100 ng/mL albendazole sulfoxide were fed to mosquitoes concomitantly with *P. falciparum* gametocytes. Kobylinski and others⁸⁰ showed a sporontocidal effect of ivermectin at the human-relevant, mosquito-sublethal concentration of 10.7 ng/mL. The concentration of albendazole sulfoxide used in the coingestion experiment was estimated from human pharmacokinetic data at the time point when 10.7 ng/mL ivermectin is present in an orally treated human approximately 21 hours post-ingestion.^{89,90}

TABLE 1

Effect of albendazole sulfoxide on *P. falciparum* sporogony in *An. gambiae*

Stage* (DPI)	Control (0)§	ALB SOx (100)	ALB SOx (1,000)
Oocyst (7)			
Prevalence† mean (SEM)	85.19 (3.42)	86.79 (3.29)	73.45 (4.15)
χ^2 value	Reference	0.8269	1.3757
P value	Reference	0.4604	0.2701
N	Reference	219	210
Intensity‡ mean (SEM)	15.60 (1.79)	17.83 (2.02)	17.68 (1.99)
P value	Reference	0.2716	0.4826
N	Reference	184	174
Sporozoite (14)			
Prevalence mean (SEM)	82.61 (3.95)	78.31 (4.52)	77.27 (4.47)
χ^2 value	Reference	1.8260	0.6950
P value	Reference	0.1947	0.4497
N	Reference	176	180

ALB Sox = albendazole sulfoxide; DPI = days post-infection.

* *P. falciparum* stage investigated.

† Prevalence rates compared by Fisher's exact test.

‡ Oocyst intensity compared by Mann-Whitney U test.

§ Treatments (nanograms per milliliter).

Albendazole sulfoxide at 1,000 or 100 ng/mL concentrations did not alter the sporogony of *P. falciparum* in *An. gambiae* (Table 1). Albendazole sulfoxide did not inhibit the sporontocidal effect of ivermectin as oocyst ($\chi^2 = 0.2485$, $P = 0.6912$, $N = 235$), sporozoite prevalence ($\chi^2 = 0.2462$, $P = 0.6635$, $N = 189$), and oocyst intensity ($P = 0.5851$, $N = 133$) did not differ between the ivermectin and ivermectin plus albendazole sulfoxide treatment groups (Table 2). We previously showed that albendazole sulfoxide at human-relevant concentrations did not reduce the survivorship or alter the refeeding frequency of *An. gambiae*,⁷⁸ and the addition of albendazole sulfoxide to ivermectin-containing blood meals did not alter mosquito lethal effects of ivermectin at human-relevant concentrations.⁹¹ Although coadministration of albendazole and ivermectin did not seem to enhance the mosquito-lethal, sublethal, or sporontocidal effects of ivermectin, it is important to note that it does not inhibit these phenomena. Because albendazole does not alter the systemic exposure of ivermectin,^{92–94} it is likely that coadministration of these drugs

TABLE 2

The effect of ivermectin and albendazole sulfoxide on *P. falciparum* sporogony in *An. gambiae* treatments

Stage (DPI)	Control	IVM	IVM and ALB SOx
Oocyst (7)			
Prevalence mean (SEM)	73.96 (4.48)	57.14 (4.54)	60.34 (4.54)
χ^2 value	Reference	8.4717	4.3705
P value	Reference	0.0004*	0.0413*
N	Reference	215	212
Intensity mean (SEM)	14.11 (2.435)	16.38 (2.255)	12.67 (1.371)
P value	Reference	0.0708	0.0641
N	Reference	134	141
Sporozoite (14)			
Prevalence mean (SEM)	76.84 (4.33)	50.0 (5.21)	53.61 (5.06)
χ^2 value	Reference	14.5523	11.4309
P value	Reference	< 0.0001*	< 0.0001*
N	Reference	187	192

ALB Sox = albendazole sulfoxide; DPI = days post-infection; IVM = ivermectin.

* Results are significant.

by MDA would produce the same impact on *Plasmodium* transmission as ivermectin alone but would maximize impact against STHs.

To assess whether albendazole coadministered with ivermectin during MDA alters the mosquito-lethal effect of ivermectin MDA, *An. gambiae* s.l. survivorship data from APOC-coordinated ivermectin (150 µg/kg) MDAs from Senegal in 2008 and 2009¹⁶ were compared with survivorship results from GPELF-coordinated ivermectin (150 µg/kg) plus albendazole (400 mg) MDAs from Liberia and Burkina Faso in 2013. Blood-fed *Anopheles* were collected by backpack aspiration from peoples' huts at multiple time points before and after MDAs and held in an insectary for 5 days post-collection while survivorship was observed daily, which was described in the work by Sylla and others.¹⁶ The survivorship rates of *An. gambiae* s.l. collected before MDA and up to 1 week after MDA were compared using a χ^2 test. Both MDA regimens significantly reduced *An. gambiae* s.l. survivorship: by 31% in ivermectin-treated villages (pre-MDA: 80.99 ± 1.34%; post-MDA: 50.0 ± 2.54%; $\chi^2 = 125.55$, $P < 0.001$, $N = 1,240$) and 29% in ivermectin plus albendazole-treated villages (pre-MDA: 85.38 ± 2.04%; post-MDA: 56.29 ± 3.84%; $\chi^2 = 113.03$, $P < 0.001$, $N = 777$). There was not a significant difference in *An. gambiae* s.l. survivorship either before ($\chi^2 = 2.64$, $P = 0.1044$, $N = 1,153$) or after ($\chi^2 = 0.45$, $P = 0.503$, $N = 864$) MDAs between the ivermectin- and ivermectin plus albendazole-treated villages. This field evidence shows that ivermectin plus albendazole coadministration does not alter ivermectin-induced *An. gambiae* s.l. mortality.

Although repeated ivermectin MDAs may suppress *Plasmodium* transmission, this administration alone is not enough to clear the infectious human reservoir of *Plasmodium* parasites. Artemisinin-based combination therapies (ACTs) are currently the most effective antimalarial drugs. The combination of ivermectin MDAs with ACT MDA or mass screening and treatment with ACT approaches would maximize *Plasmodium* transmission control efforts by simultaneously targeting vector and human reservoirs. If albendazole were coadministered with ivermectin MDAs for STH and malaria transmission control, then the safety and efficacy of this combination as adjuncts with ACTs must be assessed for both *Plasmodium* and STHs. Coadministration of ivermectin and artemether-lumefantrine was safe and well-tolerated (Bousema T, personal communication); however, no study to date has investigated the safety and efficacy of ivermectin, albendazole, and ACTs in combination. As with all MDA programs, monitoring for adverse and severe adverse events after MDAs should occur, especially when novel drug combinations are used.

IVERMECTIN AND ALBENDAZOLE MDA FOR STH TRANSMISSION CONTROL

Albendazole MDA programs targeting STHs in Kenya, China, and Uganda have shown a significant decrease in intensity and prevalence of STH infections.^{95,96} However, sustainable control of STHs is not possible with a single MDA because of high reinfection rates due to the fact that eggs and/or larvae present in soil are not affected by treatment of humans.^{97,98} Although MDAs can have an immediate impact on STH prevalence rates,^{99,100} reinfection of STHs can occur within 6–9 months post-MDA depending on a multitude of

factors, including previous STH prevalence in an area, sanitation infrastructure, community personal hygiene standards, and efficacy of albendazole for the treatment of trichuriasis and hookworm.^{101–104} As stated previously, ivermectin MDAs for *Plasmodium* transmission control in many endemic areas will have to be performed repeatedly during malaria transmission seasons to have a sustained impact on *Plasmodium* transmission.^{16,17} If albendazole was coadministered with ivermectin during these repeated MDAs for *Plasmodium* transmission control, then this combination could have a dramatic impact on STH transmission as well.

Repeated MDAs on their own are unlikely to result in sustainable control or elimination of STHs. For sustainable, long-term control and eventual elimination of STHs, deworming MDAs need to be combined with access to a safe water supply, provision of adequate sanitation, and improved hygiene behavior.¹⁰⁵ Combining MDAs with water, sanitation, and hygiene (WASH) programs poses a number of challenges, including coordination between the WASH and health sectors, adequate funding, political will, and availability of guidelines for combined strategies that are based on rigorous epidemiological and economic evaluation. The need for improved WASH should not be overlooked in the design of an integrated STH control–malaria elimination program that capitalizes on the synergistic effects of coadministration of albendazole and ivermectin together with more traditional malaria elimination strategies (e.g., LLINs and IRS), and additional research is required to determine the optimal approach for combining these interventions. Comprehensive strategies for community-based WASH programs that incorporate CDT, delivered in concert with hygiene promotion activities, may be ultimately more sustainable and cost-effective than uncoordinated approaches or those that only incorporate drug delivery or only target subgroups, such as school children.

A shift from annual school-based MDAs for morbidity control of STHs to more frequent population-wide MDAs for *Plasmodium* transmission control will increase resistance selection pressure on STHs. Ivermectin is currently not a frontline drug for STH treatment, but it is important to consider possible resistance development in STHs from more frequent ivermectin MDAs for *Plasmodium* transmission control. Coadministration of ivermectin and albendazole may reduce the likelihood of resistance development in STHs to either drug, because these drugs have different modes of action.^{106,107} In support, with the model organism *Caenorhabditis elegans*, ivermectin-resistant worms were not cross-resistant to albendazole.¹⁰⁸ In contrast, with the veterinary parasite *Haemonchus contortus*, ivermectin exposure in sheep led to an increase in the frequency of β -tubulin alleles, which are a determinant for benzimidazole resistance.¹⁰⁹ Recently, β -tubulin resistance alleles were identified in human *T. trichiura* that had been treated with albendazole but not ivermectin; however, the study did not compare allele frequency and treatment failure.¹¹⁰ As with all MDA disease control programs, active and routine monitoring and evaluation must be conducted to ensure that resistance does not develop in the STHs to either ivermectin or albendazole. Novel anthelmintics and drug combinations are needed to handle anthelmintic resistance issues. As these novel drugs and combinations are developed, it would be prudent to test their impact against *Anopheles* survivorship and *Plasmodium* transmission.

The cost of adding albendazole to ivermectin MDAs for *Plasmodium* transmission control should be nominal considering that albendazole costs much less than ivermectin,¹¹¹ the MDA costs would have already been accounted for, and the APOC, GPELF, and Mectizan Donation Program have already streamlined delivery methods for the two drugs.^{112–114} The apparent association between STHs and malaria infection suggests that targeting populations with high malaria prevalence with both ivermectin and albendazole for a more comprehensive treatment of STHs would be a potentially efficient use of resources. A proactive, integrated control platform that targets malaria and STHs would be extremely cost-effective, especially because malaria control receives a larger portion of donor money compared to NTD control.⁶⁸

CONCLUSIONS

The addition of albendazole to ivermectin MDAs would synergistically integrate STH and *Plasmodium* elimination efforts in the same platform. Albendazole treatment does not seem to inhibit the mosquito-lethal or sporontocidal effects of ivermectin and therefore, could be readily added to ivermectin MDAs for *Plasmodium* and STH transmission control. Repeated longitudinal coadministration of albendazole and ivermectin MDAs would cause dramatic reductions in STH prevalence and intensity, potentially limit STH drug resistance development, and reduce *Plasmodium* transmission rates. The combined effects of ivermectin and albendazole MDAs on malaria and STH transmission could lead to an overall improvement in human health and socioeconomic benefit beyond what would be expected from malaria control alone.

Received March 27, 2014. Accepted for publication June 4, 2014.

Published online July 28, 2014.

Acknowledgments: We thank the Walter Reed Army Institute of Research, Entomology Branch, Vector and Parasite Biology Department, especially Major Silas Davidson, Megan Dowler, Tatyana Savranskaya, Ale Zapata, and David Markman. A special thanks to Colonels Julia Lynch and Carl Mason for reviewing the manuscript before submission.

Financial support: Funding for laboratory investigation was provided by the Military Infectious Disease Research Program. Part of this research was performed while K.C.K. held a National Research Council Research Associateship Award at the Walter Reed Army Institute of Research. H.A. and B.D.F. acknowledge funding from National Institutes of Health Grant 1R01AI094349-01A1 and thank Benjamin Krajacich, Jacob Meyers, Nathan Grubaugh, Massamba Sylla, Moussa Sarr, Lawrence Fakoli III, Fatorma Bolay, and Roch Dabiré for their work facilitating the field collections.

Disclaimer: Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its publication. The opinions or assertions contained herein are the private views of the authors and not to be construed as official or reflecting true views of the Department of the Army or the Department of Defense.

Authors' addresses: Kevin C. Kobylinski, Entomology Department, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, E-mail: kobylinsikevin@yahoo.com. Haoues Alout and Brian D. Foy, Arthropod-Borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO, E-mails: Haoues@rams.colostate.edu and brian.foy@colostate.edu. Archie Clements, Research School of Population Health, College of Medicine Biology and Environment, The Australian National University, Canberra, ACT, Australia, E-mail: archie.clements@anu.edu. Poom Adisakwattana, Department of Helminthology, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, E-mail: poom.adi@mahidol.ac.th. Brett

E. Swierczewski, Bacterial Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, MD, E-mail: brett.e.swierczewski.mil@mail.mil. Jason H. Richardson, Armed Forces Pest Management Board, Silver Spring, MD, E-mail: Jason.h.richardson.mil@mail.mil.

REFERENCES

1. Roberts L, Enserink M, 2007. Malaria—did they really say ... eradication? *Science* 318: 1544–1545.
2. Utzinger J, 2012. A research and development agenda for the control and elimination of human helminthiasis. *PLoS Negl Trop Dis* 6: e1646.
3. Knopp S, Stothard JR, Rollinson D, Mohammed KA, Khamis IS, Marti H, Utzinger J, 2013. From morbidity control to transmission control: time to change tactics against helminths on Unguja Island, Zanzibar. *Acta Trop* 128: 412–422.
4. Molyneux DH, Nantulya VM, 2004. Linking disease control programmes in rural Africa: a pro-poor strategy to reach Abuja targets and millennium development goals. *BMJ* 328: 1129–1132.
5. Sachs JD, Hotez PJ, 2006. Fighting tropical diseases. *Science* 311: 1521.
6. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Sachs SE, Sachs JD, 2006. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria: a comprehensive pro-poor health policy and strategy for the developing world. *PLoS Med* 3: 576–584.
7. Hotez PJ, Molyneux DH, 2008. Tropical anemia: one of Africa's great killers and a rationale for linking malaria and neglected tropical disease control to achieve a common goal. *PLoS Negl Trop Dis* 2: e270.
8. Hotez PJ, Mistry N, Rubinstein J, Sachs JD, 2011. Integrating neglected tropical diseases into AIDS, tuberculosis, and malaria control. *N Engl J Med* 364: 2086–2089.
9. Smits HL, 2009. Prospects for the control of neglected tropical diseases by mass drug administration. *Expert Rev Anti Infect Ther* 7: 37–56.
10. Kelly-Hope LA, Molyneux DH, Bockarie MJ, 2013. Can malaria vector control accelerate the interruption of lymphatic filariasis transmission in Africa; capturing a window of opportunity? *Parasit Vectors* 6: e39.
11. Richards FO, Emukah E, Graves PM, Nkwocha O, Nwankwo L, Rakers L, Mosher A, Patterson A, Ozaki M, Nwoke BEB, Ukaga CN, Njoku C, Nwodu K, Obasi A, Miri ES, 2013. Community-wide distribution of long-lasting insecticidal nets can halt transmission of lymphatic filariasis in southeastern Nigeria. *Am J Trop Med Hyg* 89: 578–587.
12. Kisinza WN, Kisoka WJ, Mutalemwa PP, Njau J, Tenu F, Nyka T, Kilima SP, Magesa SM, 2008. Community directed interventions for malaria, tuberculosis and vitamin A in onchocerciasis endemic districts of Tanzania. *Tanzan J Health Res* 10: 232–239.
13. Remme JHF, Grp CDIS, 2010. Community-directed interventions for priority health problems in Africa: results of a multicountry study. *Bull World Health Organ* 88: 509–518.
14. Blackburn BG, Eigege A, Gotau H, Gerlong G, Miri E, Hawley WA, Mathieu E, Richards F, 2006. Successful integration of insecticide-treated bed net distribution with mass drug administration in Central Nigeria. *Am J Trop Med Hyg* 75: 650–655.
15. Chaccour CJ, Kobylinski KC, Bassat Q, Bousema T, Drakeley C, Alonso P, Foy BD, 2013. Ivermectin to reduce malaria transmission: a research agenda for a promising new tool for elimination. *Malar J* 12: e153.
16. Sylla M, Kobylinski KC, Gray M, Chapman PL, Sarr MD, Rasgon JL, Foy BD, 2010. Mass drug administration of ivermectin in south-eastern Senegal reduces the survivorship of wild-caught, blood fed malaria vectors. *Malar J* 9: e365.
17. Foy BD, Kobylinski KC, da Silva IM, Rasgon JL, Sylla M, 2011. Endectocides for malaria control. *Trends Parasitol* 27: 423–428.
18. Gutman J, Emukah E, Okpala N, Okoro C, Obasi A, Miri ES, Richards FO, 2010. Effects of annual mass treatment with ivermectin for onchocerciasis on the prevalence of intestinal helminths. *Am J Trop Med Hyg* 83: 534–541.
19. Olsen A, 2007. Efficacy and safety of drug combinations in the treatment of schistosomiasis, soil-transmitted helminthiasis,

- lymphatic filariasis and onchocerciasis. *Trans R Soc Trop Med Hyg* 101: 747–758.
20. Beach MJ, Streit TG, Addiss DG, Prospere R, Roberts JM, Lammie PJ, 1999. Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian schoolchildren. *Am J Trop Med Hyg* 60: 479–486.
 21. Ismail MM, Jayakody RL, 1999. Efficacy of albendazole and its combinations with ivermectin or diethylcarbamazine (DEC) in the treatment of *Trichuris trichiura* infections in Sri Lanka. *Ann Trop Med Parasitol* 93: 501–504.
 22. Belizario VY, Amarillo ME, de Leon WU, de los Reyes AE, Bugayong MG, Macatangay BJC, 2003. A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* spp. *Bull World Health Organ* 81: 35–42.
 23. Knopp S, Mohammed KA, Speich B, Hattendorf J, Khamis IS, Khamis AN, Stothard JR, Rollinson D, Marti H, Utzinger J, 2010. Albendazole and mebendazole administered alone or in combination with ivermectin against *Trichuris trichiura*: a randomized controlled trial. *Clin Infect Dis* 51: 1420–1428.
 24. Ottesen EA, Ismail MM, Horton J, 1999. The role of albendazole in programmes to eliminate lymphatic filariasis. *Parasitol Today* 15: 382–386.
 25. Mohammed KA, Deb RM, Stanton MC, Molyneux DH, 2012. Soil transmitted helminths and scabies in Zanzibar, Tanzania following mass drug administration for lymphatic filariasis—a rapid assessment methodology to assess impact. *Parasit Vectors* 5: e299.
 26. Gyapong JO, Kumaraswami V, Biswas G, Ottesen EA, 2005. Treatment strategies underpinning the global programme to eliminate lymphatic filariasis. *Expert Opin Pharmacother* 6: 179–200.
 27. Mwangi TW, Bethony JM, Brooker S, 2006. Malaria and helminth interactions in humans: an epidemiological viewpoint. *Ann Trop Med Parasitol* 100: 551–570.
 28. Brooker S, Clements ACA, Hotez PJ, Hay SI, Tatem AJ, Bundy DAP, Snow RW, 2006. The co-distribution of *Plasmodium falciparum* and hookworm among African schoolchildren. *Malar J* 5: e99.
 29. Brooker SJ, Pullan RL, Gitonga CW, Ashton RA, Kolaczinski JH, Kabatereine NB, Snow RW, 2012. *Plasmodium*-helminth coinfection and its sources of heterogeneity across East Africa. *J Infect Dis* 205: 841–852.
 30. Suputtamongkol Y, Premasathian N, Bhumimuang K, Waywa D, Nilganuwong S, Karuphong E, Anekthananon T, Wanachiwanawin D, Silpasakorn S, 2011. Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis. *PLoS Negl Trop Dis* 5: e1044.
 31. Kraivichian K, Nuchprayoon S, Sitichalernchai P, Chaicumpa W, Yentakam S, 2004. Treatment of cutaneous gnathostomiasis with ivermectin. *Am J Trop Med Hyg* 71: 623–628.
 32. Heukelbach J, Winter B, Wilcke T, Muehlen M, Albrecht S, de Oliveira FAS, Kerr-Pontes LRS, Liesenfeld O, Feldmeier H, 2004. Selective mass treatment with ivermectin to control intestinal helminthiasis and parasitic skin diseases in a severely affected population. *Bull World Health Organ* 82: 563–571.
 33. Okeibunor JC, Amuyunzu-Nyamongo M, Onyeneho NG, Tchounkeu YFL, Manianga C, Kabali AT, Leak S, 2011. Where would I be without ivermectin? Capturing the benefits of community-directed treatment with ivermectin in Africa. *Trop Med Int Health* 16: 608–621.
 34. Naing C, Whittaker MA, Nyunt-Wai V, Reid SA, Wong SF, Mak JW, Tanner M, 2013. Malaria and soil-transmitted intestinal helminth co-infection and its effect on anemia: a meta-analysis. *Trans R Soc Trop Med Hyg* 107: 672–683.
 35. Ojurongbe O, Adegbayi AM, Bolaji OS, Akindele AA, Adefioye OA, Adeyeba OA, 2011. Asymptomatic falciparum malaria and intestinal helminths co-infection among school children in Osogbo, Nigeria. *J Res Med Sci* 16: 680–686.
 36. Yatch NJ, Yi J, Agbenyega T, Turpin A, Rayner JC, Stiles JK, Ellis WO, Funkhouser E, Ehiri JE, Williams JH, Jolly PE, 2009. Malaria and intestinal helminth co-infection among pregnant women in Ghana: prevalence and risk factors. *Am J Trop Med Hyg* 80: 896–901.
 37. Adegnika AA, Ramharther M, Agnandji ST, Ngoa UA, Issifou S, Yazdanbakhsh M, Kremsner PG, 2010. Epidemiology of parasitic co-infections during pregnancy in Lambarene, Gabon. *Trop Med Int Health* 15: 1204–1209.
 38. Degarege A, Legesse M, Medhin G, Animut A, Erko B, 2012. Malaria and related outcomes in patients with intestinal helminths: a cross-sectional study. *BMC Infect Dis* 12: 291.
 39. Pullan RL, Kabatereine NB, Bukirwa H, Staedke SG, Brooker S, 2011. Heterogeneities and consequences of *Plasmodium* species and hookworm coinfection: a population based study in Uganda. *J Infect Dis* 203: 406–417.
 40. Hillier SD, Booth M, Muhangi L, Nkurunziza P, Kihembo M, Kakande M, Sewankambo M, Kizindo R, Kizza M, Muwanga M, Elliott AM, 2008. *Plasmodium falciparum* and helminth coinfection in a semiurban population of pregnant women in Uganda. *J Infect Dis* 198: 920–927.
 41. Fernandez-Nino JA, Idrovo AJ, Cucunuba ZM, Reyes-Harker P, Guerra AP, Moncada LI, Lopez MC, Barrera SM, Cortes LJ, Olivera M, Nicholls RS, 2012. Paradoxical associations between soil-transmitted helminths and *Plasmodium falciparum* infection. *Trans R Soc Trop Med Hyg* 106: 701–708.
 42. Righetti AA, Glinz D, Adiossan LG, Koua AYG, Niamke S, Hurrell RF, Wegmuller R, N'Goran EK, Utzinger J, 2012. Interactions and potential implications of *Plasmodium falciparum*-hookworm coinfection in different age groups in south-central Cote d'Ivoire. *PLoS Negl Trop Dis* 6: e1889.
 43. Midzi N, Sangweme D, Zinyowera S, Mapingure MP, Brouwer KC, Munatsi A, Mutapi F, Mudzori J, Kumar N, Woelk G, Mduluzi T, 2008. The burden of polyparasitism among primary schoolchildren in rural and farming areas in Zimbabwe. *Trans R Soc Trop Med Hyg* 102: 1039–1045.
 44. Humphries D, Mosites E, Otchere J, Twum WA, Woo L, Jones-Sampe H, Harrison LM, Bungiro RD, Benham-Pyle B, Bimi L, Edoh D, Bosompem K, Wilson M, Cappello M, 2011. Epidemiology of hookworm infection in Kintampo North Municipality, Ghana: patterns of malaria coinfection, anemia, and albendazole treatment failure. *Am J Trop Med Hyg* 84: 792–800.
 45. Boel M, Carrara VI, Rijken M, Proux S, Nacher M, Pimanpanarak M, Paw MK, Moot O, Gay H, Bailey W, Singhasivanon P, White NJ, Nosten F, McGready R, 2010. Complex interactions between soil-transmitted helminths and malaria in pregnant women on the Thai-Burmese border. *PLoS Negl Trop Dis* 4: e887.
 46. Spiegel A, Tall A, Raphenon G, Trape JF, Druilhe P, 2003. Increased frequency of malaria attacks in subjects co-infected by intestinal worms and *Plasmodium falciparum* malaria. *Trans R Soc Trop Med Hyg* 97: 198–199.
 47. Nacher M, Singhasivanon P, Yimsamran S, Manibunyon W, Thanyavanich N, Wuthisen P, Looareesuwan S, 2002. Intestinal helminth infections are associated with increased incidence of *Plasmodium falciparum* malaria in Thailand. *J Parasitol* 88: 55–58.
 48. Degarege A, Animut A, Legesse M, Erko B, 2009. Malaria severity status in patients with soil-transmitted helminth infections. *Acta Trop* 112: 8–11.
 49. Nacher M, Singhasivanon P, Gay F, Silachomroon U, Phumratanaprapin W, Looareesuwan S, 2001. Contemporaneous and successive mixed *Plasmodium falciparum* and *Plasmodium vivax* infections are associated with *Ascaris lumbricoides*: an immunomodulating effect? *J Parasitol* 87: 912–915.
 50. Bousema JT, Drakeley CJ, Mens PF, Arens T, Houben R, Omar SA, Gouagna LC, Schallig H, Sauerwein RW, 2008. Increased *Plasmodium falciparum* gametocyte production in mixed infections with *P. malariae*. *Am J Trop Med Hyg* 78: 442–448.
 51. Gnome A, Guelbeogo WM, Riehle MM, Tiono AB, Diarra A, Kabre GB, Sagnon N, Vernick KD, 2013. *Plasmodium* species occurrence, temporal distribution and interaction in a child-aged population in rural Burkina Faso. *Malar J* 12: e67.
 52. McKenzie FE, Jeffery GM, Collins WE, 2002. *Plasmodium malariae* infection boosts *Plasmodium falciparum* gametocyte production. *Am J Trop Med Hyg* 67: 411–414.
 53. Chaorattanakawee S, Natalang O, Hananantachai H, Nacher M, Brockman A, Nosten F, Looareesuwan S, Patarapotikul J, 2003. *Trichuris trichiura* infection is associated with the multiplicity of *Plasmodium falciparum* infections, in Thailand. *Ann Trop Med Parasitol* 97: 199–202.

54. Nacher M, Singhasivanon P, Silachamroon U, Treeprasertsuk S, Krudsood S, Gay F, Mazier D, Looareesuwan S, 2001. Association of helminth infections with increased gametocyte carriage during mild falciparum malaria in Thailand. *Am J Trop Med Hyg* 65: 644–647.
55. Nacher M, 2012. Helminth-infected patients with malaria: a low profile transmission hub? *Malar J* 11: e376.
56. Kirwan P, Asaolu SO, Molloy SF, Abiona TC, Jackson AL, Holland CV, 2009. Patterns of soil-transmitted helminth infection and impact of four-monthly albendazole treatments in preschool children from semi-urban communities in Nigeria: a double-blind placebo-controlled randomised trial. *BMC Infect Dis* 9: e20.
57. Kirwan P, Jackson AL, Asaolu SO, Molloy SF, Abiona TC, Bruce MC, Ranford-Cartwright L, O'Neill SM, Holland CV, 2010. Impact of repeated four-monthly anthelmintic treatment on *Plasmodium* infection in preschool children: a double-blind placebo-controlled randomized trial. *BMC Infect Dis* 10: e277.
58. Brutus L, Watier L, Briand V, Hanitrasoamampionona V, Razanatsorilala H, Cot M, 2006. Parasitic co-infections: Does *Ascaris lumbricoides* protect against *Plasmodium falciparum* infection? *Am J Trop Med Hyg* 75: 194–198.
59. Brutus L, Watier L, Hanitrasoamampionona V, Razanatsorilala H, Cot M, 2007. Confirmation of the protective effect of *Ascaris lumbricoides* on *Plasmodium falciparum* infection: results of a randomized trial in Madagascar. *Am J Trop Med Hyg* 77: 1091–1095.
60. Le Hesran JY, Akiana J, El Ndiaye HM, Dia M, Senghor P, Konate L, 2004. Severe malaria attack is associated with high prevalence of *Ascaris lumbricoides* infection among children in rural Senegal. *Trans R Soc Trop Med Hyg* 98: 397–399.
61. Nacher M, 2008. Worms and malaria: blind men feeling the elephant? *Parasitology* 135: 861–868.
62. Nacher M, 2011. Interactions between worms and malaria: good worms or bad worms? *Malar J* 10: e259.
63. Nacher M, Singhasivanon P, Gay F, Phumratanapapin W, Silachamroon U, Looareesuwan S, 2001. Association of helminth infection with decreased reticulocyte counts and hemoglobin concentration in Thai falciparum malaria. *Am J Trop Med Hyg* 65: 335–337.
64. Midzi N, Mtapuri-Zinyowera S, Mapingure MP, Sangweme D, Chirehwa MT, Brouwer KC, Mudzori J, Hlerema G, Mutapi F, Kumar N, Mduluza T, 2010. Consequences of polyparasitism on anaemia among primary school children in Zimbabwe. *Acta Trop* 115: 103–111.
65. Yatch NJ, Jolly PE, Funkhouser E, Agbenyega T, Rayner JC, Ehiri JE, Turpin A, Stiles JK, Ellis WO, Jiang Y, Williams JH, 2010. The effect of malaria and intestinal helminth coinfection on birth outcomes in Kumasi, Ghana. *Am J Trop Med Hyg* 82: 28–34.
66. Taylor-Robinson DC, Jones AP, Garner P, 2007. Deworming drugs for treating soil-transmitted intestinal worms in children: effects on growth and school performance. *Cochrane Database Syst Rev* 4: CD000371.
67. Sachs J, Malaney P, 2002. The economic and social burden of malaria. *Nature* 415: 680–685.
68. Molyneux DH, Hotez PJ, Fenwick A, 2005. "Rapid-impact interventions": how a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. *PLoS Med* 2: 1064–1070.
69. Christian P, Khatry SK, West KP, 2004. Antenatal anthelmintic treatment, birthweight, and infant survival in rural Nepal. *Lancet* 364: 981–983.
70. Ndyomugenyi R, Kabatereine N, Olsen A, Magnussen P, 2008. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi District, western Uganda. *Am J Trop Med Hyg* 79: 856–863.
71. Gyapong JO, Chinbuah MA, Gyapong M, 2003. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. *Trop Med Int Health* 8: 1093–1101.
72. Hibbs RE, Gouaux E, 2011. Principles of activation and permeation in an anion-selective Cys-loop receptor. *Nature* 474: 54–60.
73. Kane NS, Hirschberg B, Qian S, Hunt D, Thomas B, Brochu R, Ludmerer SW, Zheng YC, Smith M, Arena JP, Cohen CJ, Schmatz D, Warmke J, Cully DF, 2000. Drug-resistant *Drosophila* indicate glutamate-gated chloride channels are targets for the antiparasitics nodulisporic acid and ivermectin. *Proc Natl Acad Sci USA* 97: 13949–13954.
74. Nasveld P, Russell B, Kotecka B, Rieckmann K, 2003. Lack of *in vitro* effect of ivermectin on *Plasmodium falciparum*. *South-east Asian J Trop Med Public Health* 34: 552–553.
75. Lariviere M, Beauvais B, Aziz M, Garin YJF, Abeloos J, Derouin F, Bamba M, Bosseboeuf C, Ferlytherizol M, Sarfati C, Basset D, Basset A, Toure Y, Song D, Gaxotte P, 1989. Study in Ivory Coast (1985–1987) of the efficacy and tolerance of ivermectin (Mectizan) in human onchocerciasis. 1. A double-blind comparative study of 200 patients treated with a single oral dose of 100 mcg/kg, 150 mcg/kg or 200 mcg/kg. *Bull Soc Pathol Exot* 82: 35–47.
76. Fritz ML, Siegert PY, Walker ED, Bayoh MN, Vulule JR, Miller JR, 2009. Toxicity of bloodmeals from ivermectin-treated cattle to *Anopheles gambiae* s.l. *Ann Trop Med Parasitol* 103: 539–547.
77. Chaccour C, Lines J, Whitty CJM, 2010. Effect of ivermectin on *Anopheles gambiae* mosquitoes fed on humans: the potential of oral insecticides in malaria control. *J Infect Dis* 202: 113–116.
78. Kobylinski KC, Deus KM, Butters MP, Hongyu T, Gray M, da Silva IM, Sylla M, Foy BD, 2010. The effect of oral anthelmintics on the survivorship and re-feeding frequency of anthropophilic mosquito disease vectors. *Acta Trop* 116: 119–126.
79. Butters MP, Kobylinski KC, Deus KM, da Silva IM, Gray M, Sylla M, Foy BD, 2012. Comparative evaluation of systemic drugs for their effects against *Anopheles gambiae*. *Acta Trop* 121: 34–43.
80. Kobylinski KC, Foy BD, Richardson JH, 2012. Ivermectin inhibits the sporogony of *Plasmodium falciparum* in *Anopheles gambiae*. *Malar J* 11: e381.
81. Kobylinski KC, Sylla M, Chapman PL, Sarr MD, Foy BD, 2011. Short report: ivermectin mass drug administration to humans disrupts malaria parasite transmission in Senegalese villages. *Am J Trop Med Hyg* 85: 3–5.
82. Alonso PL, Besansky NJ, Burkot TR, Collins FH, Hemingway J, James AA, Lengeler C, Lindsay S, Liu QY, Lobo NF, Mnzava A, Tanner M, Zwiebel L, Consultative Group on Vector Control, 2011. A research agenda for malaria eradication: vector control. *PLoS Med* 8: e1000401.
83. Dieckmann-Schuppert A, Franklin RM, 1989. Compounds binding to cytoskeletal proteins are active against *Plasmodium falciparum* *in vitro*. *Cell Biol Int Rep* 13: 411–418.
84. Skinner-Adams TS, Davis TME, Manning LS, Johnston WA, 1997. The efficacy of benzimidazole drugs against *Plasmodium falciparum* *in vitro*. *Trans R Soc Trop Med Hyg* 91: 580–584.
85. Dow GS, Reynoldson JA, Thompson RCA, 1998. *Plasmodium berghei*: *in vivo* efficacy of albendazole in different rodent models. *Exp Parasitol* 88: 154–156.
86. Dow GS, O'Hara AJ, Newton SC, Reynoldson JA, Thompson RCA, 2000. *Plasmodium berghei*: the antimalarial activity of albendazole in rats is mediated via effects on the hematopoietic system. *Exp Parasitol* 94: 259–263.
87. Bell A, 1998. Microtubule inhibitors as potential antimalarial agents. *Parasitol Today* 14: 234–240.
88. Kappes B, Rohrbach P, 2007. Microtubule inhibitors as a potential treatment for malaria. *Future Microbiol* 2: 409–423.
89. Chen XY, Zhao LY, Xu HY, Zhong DF, 2004. Simultaneous determination of albendazole and its major active metabolite in human plasma using a sensitive and specific liquid chromatographic-tandem mass spectrometric method. *J Pharm Biomed Anal* 35: 829–836.
90. El-Tahtawy A, Glue P, Andrews EN, Mardekian J, Amsden GW, Knirsch CA, 2008. The effect of azithromycin on ivermectin pharmacokinetics: a population pharmacokinetic model analysis. *PLoS Negl Trop Dis* 2: e236.
91. Kobylinski KC, 2011. Ivermectin mass drug administration to humans for malaria parasite transmission control. Ph.D. dissertation. Fort Collins, CO: Department of Microbiology, Immunology and Pathology, Colorado State University.

92. Awadzi K, Hero M, Opoku NO, Buttner DW, Coventry PA, Prime MA, Orme ML, Edwards G, 1994. The chemotherapy of onchocerciasis. 17. A clinical evaluation of albendazole in patients with onchocerciasis—effects of food and pretreatment with ivermectin on drug response and pharmacokinetics. *Trop Med Parasitol* 45: 203–208.
93. Awadzi K, Addy ET, Opoku NO, Plenge-Bonig A, Buttner DW, 1995. The chemotherapy of onchocerciasis XX: ivermectin in combination with albendazole. *Trop Med Parasitol* 46: 213–220.
94. Awadzi K, Edwards G, Duke BOL, Opoku NO, Attah SK, Addy ET, Ardrey AE, Quartey BT, 2003. The co-administration of ivermectin and albendazole safety, pharmacokinetics and efficacy against *Onchocerca volvulus*. *Ann Trop Med Parasitol* 97: 165–178.
95. Peterson LS, Ondiek M, Oludhe DO, Naul BA, Vermund SH, 2011. Effectiveness of a school-based deworming campaign in rural Kenya. *J Trop Pediatr* 57: 461–463.
96. Zhang Y, Koukounari A, Kabatereine N, Fleming F, Kazibwe F, Tukahebwa E, Stothard JR, Webster JP, Fenwick A, 2007. Parasitological impact of 2-year preventive chemotherapy on schistosomiasis and soil-transmitted helminthiasis in Uganda. *BMC Med* 5: e27.
97. Knopp S, Steinmann P, Keiser J, Utzinger J, 2012. Nematode infections soil-transmitted helminths and *Trichinella*. *Infect Dis Clin North Am* 26: 341–358.
98. Barry MA, Simon GG, Mistry N, Hotez PJ, 2013. Global trends in neglected tropical disease control and elimination: impact on child health. *Arch Dis Child* 98: 635–641.
99. Humphries D, Nguyen S, Boakye D, Wilson M, Cappello M, 2012. The promise and pitfalls of mass drug administration to control intestinal helminth infections. *Curr Opin Infect Dis* 25: 584–589.
100. Prichard RK, Basanez MG, Boatn BA, McCarthy JS, Garcia HH, Yang GJ, Sripa B, Lustigman S, 2012. A research agenda for helminth diseases of humans: intervention for control and elimination. *PLoS Negl Trop Dis* 6: e1549.
101. Hall A, Hewitt G, Tuffrey V, de Silva N, 2008. A review and meta-analysis of the impact of intestinal worms on child growth and nutrition. *Matern Child Nutr* 4 (Suppl 1): 118–236.
102. Vercruysse J, Behnke JM, Albonico M, Ame SM, Angebault C, Bethony JM, Engels D, Guillard B, Hoa NTV, Kang G, Kattula D, Kotze AC, McCarthy JS, Mekonnen Z, Montresor A, Periago MV, Sumo L, Tchuente LAT, Thach DTC, Zeynudin A, Levecke B, 2011. Assessment of the anthelmintic efficacy of albendazole in school children in seven countries where soil-transmitted helminths are endemic. *PLoS Negl Trop Dis* 5: e948.
103. Keiser J, Utzinger J, 2008. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA* 299: 1937–1948.
104. Geary TG, Woo K, McCarthy JS, Mackenzie CD, Horton J, Prichard RK, de Silva NR, Olliaro PL, Lazdins-Helds JK, Engels DA, Bundy DA, 2010. Unresolved issues in anthelmintic pharmacology for helminthiasis of humans. *Int J Parasitol* 40: 1–13.
105. Campbell SJ, Savage GB, Gray DJ, Atkinson JA, Soares Magalhaes RJ, Nery SV, McCarthy JS, Velleman Y, Wicken JH, Traub RJ, Williams GM, Andrews RM, Clements AC, 2014. Water, Sanitation and Hygiene (WASH): a critical component for sustainable soil-transmitted helminth and schistosomiasis control. *PLoS Negl Trop Dis* 8: e2651.
106. Cully DF, Vassilatis DK, Liu KK, Parens PS, Vanderploeg LHT, Schaeffer JM, Arena JP, 1994. Cloning of an ivermectin-sensitive glutamate-gated chloride channel from *Caenorhabditis elegans*. *Nature* 371: 707–711.
107. Borgers M, Denollin S, Debrabander M, Thienpont D, 1975. Influence of anthelmintic mebendazole on microtubules and intracellular organelle movement in nematode intestinal cells. *Am J Vet Res* 36: 1153–1166.
108. James CE, Davey MW, 2009. Increased expression of ABC transport proteins is associated with ivermectin resistance in the model nematode *Caenorhabditis elegans*. *Int J Parasitol* 39: 213–220.
109. Mottier MD, Prichard RK, 2008. Genetic analysis of a relationship between macrocyclic lactone and benzimidazole anthelmintic selection on *Haemonchus contortus*. *Pharmacogenet Genomics* 18: 129–140.
110. Diawara A, Drake LJ, Suswillo RR, Kihara J, Bundy DAP, Scott ME, Halpenny C, Stothard JR, Prichard RK, 2009. Assays to detect beta-tubulin codon 200 polymorphism in *Trichuris trichiura* and *Ascaris lumbricoides*. *PLoS Negl Trop Dis* 3: e397.
111. Goldman AS, Guisinger VH, Aikins M, Amarillo MLE, Belizario VY, Garshong B, Gyapong J, Kabali C, Kamal HA, Kanjilal S, Kyelem D, Lizardo J, Malecela M, Mubyazi G, Nitiema PA, Ramzy RMR, Streit TG, Wallace A, Brady MA, Rheingans R, Ottesen EA, Haddix AC, 2007. National mass drug administration costs for lymphatic filariasis elimination. *PLoS Negl Trop Dis* 1: e67.
112. Burnham G, Mebrahtu T, 2004. Review: The delivery of ivermectin (Mectizan (R)). *Trop Med Int Health* 9: A26–A44.
113. Amazigo UV, Brieger WR, Katabarwa M, Akogun O, Ntep M, Boatn B, N'Doyo J, Noma M, Seketeli A, 2002. The challenges of community-directed treatment with ivermectin (CDTI) within the African Programme for Onchocerciasis Control (APOC). *Ann Trop Med Parasitol* 96: 41–58.
114. Gustavsen KM, Bradley MH, Wright AL, 2009. GlaxoSmithKline and Merck: private-sector collaboration for the elimination of lymphatic filariasis. *Ann Trop Med Parasitol* 103: S11–S15.